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Positive Fluid Balance and Association with Post-Traumatic Acute Kidney Injury

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Abstract

Background: Acute kidney injury (AKI) is common in severely injured trauma patients and is associated with poor outcomes. A positive fluid balance is associated with AKI and poor long-term renal outcomes among general intensive care unit (ICU) and cardiac surgery patients.

Currently, the optimal endpoint of resuscitation of severely injured trauma patients is unknown, which may result in excess fluid administration. We hypothesized that positive fluid balance is common after severe trauma and is associated with increased AKI development.

Design: A cohort study of adult (> 16 years) trauma patients requiring ICU admission from January 2017 to June of 2017 was conducted. Patients were excluded for early death, rhabdomyolysis, or prior history of end-stage renal disease or congestive heart failure. AKI within 7 days of admission was defined according to Kidney Disease Improving Global Outcomes creatinine-based criteria. Univariate and multivariable analyses were performed.

Results: Of 364 patients, 74% were male. The median age was 41 years (IQR 27-59) and the median injury severity score (ISS) was 18 (IQR 10-29). Positive fluid balance (>2L) was observed in 49% of patients. AKI was diagnosed in 105 (29%) patients. After adjustment, there was an

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increased risk of AKI with a positive fluid balance >2L (RR 1.98 (95% CI 1.24-3.17)). Additionally, the risk of AKI incrementally increased by 1.22 with each liter fluid positive above a zero balance (95% CI 1.11-1.34).

Conclusions: Positive fluid balance in excess of 2L at 48-hours occurs in half of severely injured trauma patients and fluid positivity is independently and incrementally associated with AKI development. Fluid responsiveness should be investigated as an end point of post-traumatic resuscitation to prevent unnecessary fluid administration and subsequent AKI.

Graphical Abstract

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Precis:

A positive fluid balance occurred in half of severely injured trauma patients at 48 hours after arrival. Furthermore, a positive fluid balance is independently and incrementally associated with acute kidney injury development. Excess fluid administration should be avoided to improve the care of severely injured trauma patients.

Keywords

AKI; Trauma; Fluid Balance

Introduction

Critically ill trauma patients frequently require blood and fluid administration to re-establish adequate intravascular volume. [1] However, less than 50% of critically ill, hemodynamically unstable patients are fluid responsive, defined by an increase in stroke volume of 10-15% following a fluid challenge. [2] Fluid administration in patients who are not fluid responsive can be harmful, resulting in tissue edema, impaired oxygen and metabolite diffusion, and damaged cell-cell interactions. [3, 4] Encapsulated organs, such as the kidneys, are particularly sensitive to interstitial edema, which increases venous pressure and decreases glomerular filtration rate (GFR). [4-6] Renal dysfunction in the setting of excess fluid administration has been demonstrated in the absence of intra-abdominal hypertension in a variety of clinical scenarios including sepsis and after cardiovascular surgery. [4, 7, 8] Liberal fluid administration and fluid positivity after trauma has been

shown to increase mortality and worsen organ dysfunction such as pulmonary edema, coagulopathy, ileus, abdominal compartment syndrome, and delayed wound healing. [9, 10] However, the relationship between fluid positivity and renal dysfunction after trauma has not previously been evaluated.

Acute kidney injury (AKI) after trauma is probably multi-factorial due to hemorrhage and hypoperfusion, reperfusion injury, rhabdomyolysis, systemic inflammation due to trauma, and nephrotoxin exposure. AKI after trauma is independently associated with mortality, multiple organ dysfunction, length of stay, cost of care, and discharge to a destination other than home.[11-17]

While acute post-injury resuscitation strategies for patients with severe trauma have evolved over the past few decades to include decreased crystalloid resuscitation, balanced transfusions of blood components, and permissive hypotension, the optimal endpoints of resuscitation are unknown. [18] Administration of excess fluids remains a potentially modifiable risk factor for poor outcomes including AKI after trauma.

The objective of this study was to explore the relationship between fluid balance and post-traumatic acute kidney injury. The hypotheses evaluated in this study were that positive fluid balance is common and independently associated with AKI development after severe trauma.

Methods

A retrospective cohort study was conducted at the Red Duke Trauma Institute at Memorial Hermann Hospital, Texas Medical Center, a high-volume, level 1 trauma center in Houston, Texas, USA. The McGovern Medical School at UTHealth institutional review board approved this study. Adult (≥ 16 years) trauma patients requiring intensive care unit (ICU) admission from January 2017 through June 2017 were included. Patients who died within 48 hours were excluded due to the competing outcomes of death and AKI. Patients with pre-existing end-stage renal disease, congestive heart failure, severe burns >20% total body surface area, and rhabdomyolysis were excluded. [19, 20] The Strengthening of the Reporting of Observational Studies in Epidemiology guidelines for observational studies were followed. [21]

Demographic characteristics, past medical history, injury details, length-of-stay, ventilator days, and in-hospital mortality were obtained from the institution's prospectively maintained trauma registry. Laboratory results, quantity of fluids and type of fluids administered were extracted from the medical record. Fluid balances were computed by subtracting all outputs from all intakes. Insensible losses were not considered. Indication for fluid administration was determined by review of inpatient physician documentation. Patients were split into three groups based on 48-hour fluid balance: fluid negative if patients had a fluid balance less than -2 liters, euvoolemia if patients had a fluid balance between -2 and +2 liters, and fluid positive if patients had a fluid balance above +2 liters. Although a fluid balance of zero is recommended for critically ill patients by the World Society of the Abdominal Compartment Syndrome [22] and other authors [23], fluid balance within 2 liters was

chosen as an indicator of general euvoolemia to allow for inaccuracies in blood loss estimations and for insensible losses not captured within the data. [24] The time point of 48-hours was chosen to include expected duration and completion of the acute resuscitation phase. Fluid overload, which is the percentage of fluid accumulation, was calculated for each patient in the cohort by dividing the cumulative fluid balance in liters by the patient's arrival body weight and then multiplying by 100%. [23] Fluid overload was used in a subgroup analysis in lieu of fluid balance. Finally, those who were most likely to have a documented indication for fluid administration, those fluid positive 5 liters or greater, were closely reviewed. Indications were grouped by hemorrhage, systemic inflammatory response syndrome, and unknown.

Outcome Measures:

This study assessed two outcomes: AKI incidence and in-hospital mortality. AKI diagnosis was made and stages were assigned based on the current guidelines published by the Kidney Disease Improving Global Outcomes (KDIGO) group. [25] The highest creatinine within one week of admission was compared to the first hospitalization creatinine in order to determine the increase from baseline. [12] A patient was diagnosed with AKI if they met criteria for AKI stage 1 or higher within the first 7 days from admission. According to the KDIGO guidelines, stage 1 should be assigned if there was an increase in serum creatinine by 0.3 mg/dl within 48 hours or an increase in serum creatinine to 1.5 times reference within 7 days. Patients requiring dialysis within 7 days were assigned as AKI stage 3. AKI incidence was defined as the proportion of patients with AKI among total included patients.

Statistical Analysis:

Incidence of AKI, demographics, and outcomes were compared between the fluid balance groups. Continuous variables were presented as medians and interquartile ranges (IQRs). Chi-square and Wilcoxon rank-sum tests were utilized to compare categorical and continuous demographic data and outcomes respectively. Kruskal-Wallis rank sum test was utilized to compare continuous data between multiple groups. Multivariable Poisson regression with robust error variance was utilized to assess the relationship between AKI and in-hospital mortality for each of the reference estimates. [26, 27] Log-binomial models were fit as an alternative. Best model fit was determined by minimization of AIC and Vuong comparison of likelihood ratios. All associations were reported as incidence risk ratios with robust confidence intervals. Variables associated with AKI were chosen a priori and included in the multivariable model: age, sex, arrival systolic blood pressure, injury severity score, and arrival base excess. Patients with missing data were excluded from the multivariable analyses. A sensitivity analysis was performed using fluid overload instead of fluid balance in the multivariable model. Probability values of 0.05 or less were considered significant. All data analyses were completed using R version 3.53 (R Core Team. 2013. *R: A language and environment for statistical computing*. R Foundation for Statistical Computing, Vienna, Austria).

Results

There were 434 patients admitted to the trauma ICU over the study period. Seventy patients were excluded, 27 for death within 48 hours, 18 for a history of end-stage renal disease or congestive heart failure, and 25 for rhabdomyolysis, resulting in 364 patients remaining for analysis (Figure 1). One or more data points was missing in 8 (2%) patients. At 48 hours from admission, 179 (49%) patients were fluid positive. Only 8 (2%) patients were fluid negative at 48 hours, and the remaining 177 (49%) were euvolemic. Most patients were male and severely injured, with a median age of 41. (Table 1) Because the characteristics of fluid negative and euvolemic patients were similar, these were combined for further analysis. On univariate analysis, patients who were fluid positive at 48 hours presented with a lower systolic blood pressure, a lower base excess, and were more severely injured than patients who were euvolemic or fluid negative at 48 hours. AKI occurred more often in patients who were fluid positive at 48 hours. Stage 1 AKI occurred most frequently. Patients who were fluid positive had more ventilation days, longer ICU length-of-stay, and longer hospital length-of-stay. In-hospital mortality occurred in 5% of patients overall, but was more common in patients who were fluid positive.

Patients who developed AKI were older and more severely injured than those who did not develop AKI. (Table 2) Patients with AKI had a higher 48-hour fluid balance, higher percent of fluid overload, more ventilator, ICU days, and hospital days. Mortality was ten times higher in patients with AKI than those without. Additionally, mortality was highest among patients who suffered AKI stage 3. (eTable 1)

Fluid positivity and AKI:

On multivariable analysis, with fluid balance as a categorical variable, fluid positivity was independently associated with an increased risk of AKI, with a relative risk of 1.98 (95% confidence interval 1.24-3.17, $p=0.02$) (Figure 2) Older age was also independently associated with increased AKI risk (RR 1.24, 95% CI 1.08-1.41, $p=0.005$). (eTable 2) A second model was created with fluid balance as an ordinal variable, which revealed each additional positive liter of fluid balance above zero was associated with a relative risk 1.22 (95% CI 1.11-1.34) of AKI development. Higher age was again independently associated with increased AKI risk (RR 1.24, 95% CI 1.09-1.40, $p=0.005$). (eTable 2).

Fluid positivity and in-hospital mortality:

An exploratory analysis was completed to examine the relationship between fluid positivity at 48 hours and mortality. The relative risk of mortality with fluid positivity was 1.65 (95% CI 0.47-5.71, $p=0.37$). Older age and higher ISS were independently associated with increased mortality ($p<0.05$). A second analysis was completed utilizing fluid balance as an ordinal variable. The relative risk of mortality with each additional liter of fluid balance was 1.17 (0.90-1.53) Again, older age and higher ISS, were independently associated with increased mortality ($p<0.05$).

Sensitivity Analyses:

The relationship between fluid overload and AKI was explored utilizing multivariable models adjusted for age, sex, systolic blood pressure, injury severity score, arrival base excess, history of diabetes mellitus or hypertension, and trauma mechanism of injury.. Fluid overload was associated with a 1.07 RR (95% CI 1.01-1.13) of AKI. Model characteristics using fluid balance were superior to the model using fluid overload on Vuong comparison of likelihood ratios ($p=0.032$).

Indication for Fluid Administration

Of the 50 patients who were greater than 5 liters positive after 48 hours, 14 (28%) were resuscitated for ongoing hemorrhage, 11 (22%) for an inflammatory response to trauma, 1 (5%) for septic shock present on admission, and 24 (45%) for an unknown or undocumented reason. The patient resuscitated for septic shock was excluded from the descriptive analysis. (Table 3, Figure 3A) The characteristics of the fluid given to patients differed based on resuscitation indication. Patients with hemorrhage were primarily administered blood products. Patients with an inflammatory response to trauma or other indication were primarily administered crystalloids. Medications made up a consistent proportion of intake across groups. Blood loss, calculated by adding documented blood loss to chest tube and drain output, and urine output, which was routinely measured using a catheter, were the only two documented outputs. (Figure 3B) Oliguria, defined as <0.5 cc/kg/hr of the total 48-hour urine output, occurred in 5 (36%) patients with hemorrhage, 2 (18%) patients with inflammatory response to trauma, and 11 (46%) patients with undocumented reason for fluid administration. Estimated blood loss made up nearly half the fluid losses for patients with documented hemorrhage. Blood loss was a minor source of fluid loss in patients with inflammatory response to trauma and other resuscitation indications. Among patients with hemorrhage, 64% developed AKI as compared to patients with an inflammatory response (18%) or other reasons for fluid administration (29%). Additionally, among patients with hemorrhage, 36% of patients had stage 1 AKI, 7% had stage 2 AKI, and 21% had stage 3 AKI. Among patients with an inflammatory response, 100% of patients who developed AKI had stage 3 AKI.

Discussion

This cohort study showed that despite a balanced fluid resuscitation protocol, fluid positivity was common at a high-volume level 1 trauma center, occurring in half of severely injured trauma patients at 48 hours. Fluid positivity was independently and incrementally associated with acute kidney injury development. Positive fluid balance was not limited to hemorrhaging patients but also occurred in patients suffering post-traumatic inflammatory response or sepsis on arrival. The indication for resuscitation was undocumented in nearly half of patients with a fluid balance >5 liters at 48 hours.

Fluid administration is a common intervention in severely injured trauma patients. Fluid administration is used to restore stroke volume and cardiac output, which improves renal perfusion in hypovolemic patients. The traditional management paradigm for patients with AKI has involved high-volume fluid resuscitation. [4] However, there is growing evidence

that excess fluid administration may be in itself detrimental to renal function. Interstitial edema and subsequent dysfunction has been well-described in a number of other organ systems, particularly in the heart, lungs, and gastrointestinal tract. [28] Excessive interstitial edema may have significant implications for viscera surrounded by nonexpansible compartments, which includes the kidney. Increased interstitial pressure may increase intracapsular pressure, reduce blood flow, and subsequently result in kidney damage and dysfunction. This was demonstrated in a study of healthy, euvoletic volunteers who underwent crystalloid infusion. Imaging and renal function tests completed after crystalloid infusion of only two liters demonstrated a decrease in renal artery flow and increase in renal volume, suggesting renal tissue edema. [29]

Patients who have suffered severe trauma may require more fluid administration due to traumatic endotheliopathy, which is present in up to 80% of injured patients with hemorrhagic shock. [30] Traumatic endotheliopathy results in the loss of vascular integrity and may result in inadequate intravascular retention and subsequent interstitial fluid accumulation. [31] Injured patients with endotheliopathy are more likely to suffer AKI and acute lung injury, both of which are closely linked to fluid status. [30] Models of venous outflow obstruction may lead to similar interstitial fluid accumulation. Both murine and swine models demonstrated worse renal damage with renal vein clamping than with renal artery clamping, suggesting that venous congestion secondary to intracapsular or intraabdominal hypertension may result in more severe kidney damage and dysfunction than hypovolemia. [32, 33] Although numerous investigations are ongoing, further work is needed to evaluate the in-vivo effects of post-traumatic endotheliopathy on kidney dysfunction.

The relationship between AKI and excessive fluid administration is muddled by oliguria, which may result from severe renal dysfunction and was present in 36% of patients more than 5L positive in the present study. A secondary analysis of the Nefrologia e Cura Intensiva (NEFROINT) study found both oliguria and fluid overload to be independently associated with increased mortality in patients with AKI. [34] A meta-analysis of 9 trials of dynamic evaluation of volume responsiveness in patients with septic shock has shown to reduce renal complications (RR 0.54, 95% CI 0.28-1.04). [35] In a meta-analysis of 8 randomized trials of goal-directed fluid therapy in surgical populations, there was decreased AKI development in patients who received the goal-directed therapy (RR 0.47, 95% CI 0.29-0.76). [36] In the studies included, there were no differences in the cumulative fluid balance between groups, suggesting that goal-directed therapy may trigger appropriate escalation and discontinuation of fluid administration, resulting in superior renal outcomes.

Fluid balance is a practice-dependent and potentially modifiable risk factor for poor outcomes, which has been demonstrated in this study and across other populations. Currently, there is little known about goal-directed care and optimal end-points of resuscitation in the severely injured trauma population. [18] There are well-established guidelines regarding treatment of the acutely hemorrhaging patient, but little is known regarding the treatment of the severely-injured patient who either never suffered massive blood loss or who has had hemorrhage controlled and adequate blood products administered. Additionally, the successful differentiation between systemic inflammatory response to

trauma and hemorrhage by clinicians is unknown. Systemic inflammatory response to trauma may present as a distributive shock and therapies for its treatment and immune modulation are undefined, making treatment of these patients particularly challenging. [37]

The implementation of damage-control resuscitation and balanced transfusion has resulted in improved survival. [38] With increasing survivorship from severe injury, avoidance of iatrogenic injury is paramount. This study demonstrated that positive fluid balance is independently associated with AKI development after trauma and suggests that a significant portion of administered fluids may be avoidable in the patients who were most fluid positive at 48 hours. Further evaluation into resuscitation practices in the non-hemorrhaging trauma patient and better clinical characterization of systemic inflammatory response to trauma may improve purposeful treatment of this condition. Furthermore, identification of accurate end-points of resuscitation may aid in efficient discontinuation of unnecessary fluid administration.

Limitations:

Several limitations exist in this study. First, hourly urine output was not considered for AKI diagnosis and staging. [12, 15, 16] There are significant limitations in the accuracy of urine output data retrospectively collected. The effect of this exclusion likely resulted in an underestimation of AKI incidence. Prospective studies of AKI after trauma should incorporate hourly urine output into AKI diagnostic criteria to optimize value of the diagnosis. Similarly, fluid balance data are subjected to some of the inaccuracies previously mentioned.

Second, the definition of AKI is widely debated, specifically after trauma due to the widespread lack of a true baseline available for each patient which was drawn during a recent, healthy state. To minimize the inclusion of erroneous AKI diagnoses due to a mildly elevated creatinine frequently seen on arrival, a strict baseline was chosen for this study: arrival creatinine. Admission creatinine was chosen to define the reference estimate, in order to ensure that the outcome would occur only after the exposure of fluid. The consequence of this decision was likely an underestimation of the true incidence of AKI, because it may have excluded patients who either had persistent AKI from arrival or who recovered quickly. The exclusion of patients who suffered early death also results in a depressed mortality rate, given that the majority of severe trauma mortality is within 24 hours of injury. [39]

Other limitations include the lack of type and dose of individual medications that may contribute to AKI development in this patient population, such as non-steroidal anti-inflammatory drugs and aminoglycoside antibiotics. Additionally, long-term renal status is unknown for this cohort due to the low rate of in-system follow up. Finally, the volume responsiveness of the study participants is unknown given that its measurement is variable and rarely documented. Administration of significant amounts of fluids may be warranted in many of the participants and future studies of resuscitation end points should closely measure and follow volume responsiveness.

Conclusions:

Fluid positivity occurred in half of severely injured trauma patients at 48 hours in this cohort study. Fluid positivity was independently and incrementally associated with AKI development. Positive fluid balance was not limited to hemorrhaging patients but also occurred in patients suffering post-traumatic inflammatory response and sepsis on arrival. Fluid responsiveness should be investigated as an end point of post-traumatic resuscitation to prevent unnecessary fluid administration and subsequent AKI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:
Flow chart of patient groups. ESRD, end stage renal disease; CHF, congestive heart failure

Figure 2:

(■) Association between fluid positivity (>2 L) and acute kidney injury (AKI) development,
 (●) association between fluid balance per liter, and AKI development.

Figure 3:
(A) Fluid intake and (B) output by resuscitation indication

Table 1:

Characteristics of Study Participants by Fluid Status

Patient characteristic	Euvolemic or fluid negative (n=185)	Fluid positive (n=179)	All patients (n=364)	p Value
Age, y, median (IQR)	42 (28-61)	40 (28-54)	41 (28-59)	0.64
Male sex, %	74	74	74	1
Race/ethnicity, %				0.58
White	47	40	44	-
Black	20	25	22	-
Hispanic	3	4	3	-
Asian	2	1	2	-
BMI, kg/m ² , median (IQR)	27 (24-31)	27 (23-30)	27 (23-30)	0.68
History of diabetes mellitus, %	0	6	3	0.003
History of hypertension, %	17	19	18	0.78
Blunt mechanism of injury, %	78	84	81	0.24
Injury severity score, median (IQR)	17 (9-25)	22 (13-29)	18 (10-29)	<0.001
Arrival systolic blood pressure, mmHg, median (IQR)	130 (110-148)	124 (108-140)	128 (109-144)	0.04
Arrival base excess, mmol/L, median (IQR)	0 (-3-0)	-1 (-6-0)	0 (-4-0)	0.003
48-hour fluid balance, L, median (IQR)	0.8 (-0.6-1.3)	3.9 (2.8-5.6)	1.9 (0.7-3.9)	<0.001
48-hour fluid overload, %, median (IQR)	0.9 (-0.7-1.6)	4.7 (3.5-7)	2.3 (0.8-4.6)	<0.001
AKI incidence, n (%)	21 (11)	40 (22)	61 (17)	0.008
Highest AKI stage, n				0.03
Stage 1	15	28	43	-
Stage 2	4	5	9	-
Stage 3	2	7	9	-
Dialysis required, n	0	6	6	0.03
Acute respiratory distress syndrome, %	0	1	1	0.47
Time on ventilator, d, median (IQR)	0 (0-1)	1 (0-3)	0 (0-2)	<0.001
ICU length-of-stay, d, median (IQR)	2 (1-5)	4 (2-9)	3 (1-6)	<0.001
Hospital length-of-stay, d, median (IQR)	8 (5-14)	11 (7-21)	9 (5-17)	<0.001
In-hospital mortality, %	3	7	5	0.14

AKI, acute kidney injury; IQR, interquartile range

Table 2:

Patient Characteristic by Acute Kidney Injury Status

Patient characteristic	No AKI (n=303)	AKI (n=61)	All patients (n=364)	p Value
Age, y, median (IQR)	39 (27-55)	49 (37-69)	41 (28-59)	<0.001
Male sex, %	74	74	74	1
Race/ethnicity, %				0.18
White	43	48	44	-
Black	23	14	22	-
Hispanic	3	5	3	-
Asian	2	0	2	-
BMI, kg/m ² , median (IQR)	27 (23-30)	28 (25-31)	27 (23-30)	0.16
History of diabetes mellitus, %	2	7	3	0.12
History of hypertension, %	16	28	18	0.05
Blunt mechanism of injury, %	79	90	81	0.07
Injury severity score, median (IQR)	17 (10-27)	22 (14-33)	18 (10-29)	0.02
Arrival systolic blood pressure, mmHg, median (IQR)	126 (110-143)	132 (102-147)	128 (109-144)	0.51
Arrival base excess, mmol/L, median (IQR)	0 (-4-0)	0 (-5-0)	0 (-4-0)	0.91
48-hour fluid balance, L, median (IQR)	1.7 (0.5-3.6)	3.1 (1.5-5.6)	1.9 (0.7-3.9)	<0.001
Fluid positive, >2 L at 48 hours, %	46	67	49	0.008
48-hour fluid overload, %, median (IQR)	2.1 (0.6-4.5)	3.9 (1.9-6.5)	2.3% (0.8-4.6)	<0.001
Acute respiratory distress syndrome, %	0	1	1	0.03
Time on ventilator, d, median (IQR)	0 (0-1)	1 (0-9)	0 (0-2)	<0.001
ICU length-of-stay, d, median (IQR)	2 (1-5)	6 (2-15)	3 (1-6)	<0.001
Hospital length-of-stay, d, median (IQR)	9 (5-15)	13 (7-25)	9 (5-17)	<0.001
In-hospital mortality, %	2	20	5	0.14

AKI, acute kidney injury; IQR, interquartile range

Table 3.

Makeup of 48-hour Fluid Balance by Resuscitation Indication

Fluid intake or output, %	Hemorrhage (n=14)	Inflammatory response (n=11)	Other (n=24)	p Value
Intake				
Transfusion	47.6 (34.3-60.8)	6.1 (1.3-1.9)	6.0 (0-26.3)	<0.001
Crystalloid or albumin	25.9 (19.5-37.7)	62.5 (41.5-69.7)	57.7 (41.8-72.8)	<0.001
Medication	9.1 (12.5-8.4)	12.5 (7.2-0.39)	8.3 (4.9-11.0)	0.09
Oral	8.8 (7.0-16.9)	13.7 (4.3-16.2)	13.8 (6.4-23.9)	0.57
Output				
Blood loss	44.0 (19.8-65.7)	8.8 (2.8-14.3)	13.0 (2.8-27.4)	0.02
Urine	47.5 (31.8-74.2)	84.9 (76.3-93.7)	83.6 (64.0-92.7)	0.02

Continuous data presented as: median (IQR)